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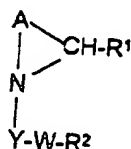
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(54) Title: HETEROCYCLIC COMPOUNDS AS INHIBITORS OF ROTAMASE ENZYMES



(1)

(57) Abstract

Compounds of formula (1) wherein R¹, Y, W, A and R² as defined above are inhibitors of rotamase enzymes in particular FKBP-12 and FKBP-52. The compounds therefore moderate neuronal regeneration and outgrowth and can be used for treating neurological disorders arising from neurodegenerative diseases and nerve damage.

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HETEROCYCLIC COMPOUNDS AS INHIBITORS OF ROTAMASE ENZYMES

This invention relates to 2-heteroaryl-pyrrolidine, -piperidine and -homopiperidine derivatives and to processes for the preparation of, intermediates used in the preparation of, compositions containing and the uses of, such derivatives.

It has been reported that the immunosuppressant FK-506 promotes neurite outgrowth in vitro in neuronal cell line and culture models (see Lyons et al, Pro. Natl. Acad. Sci., 1994, 91, 3191-95 and Snyder et al, Nature Medicine, 1995, 1, 32-37). WO-A-96/40140, WO-A-96/40633 and WO-A-97/16190 disclose compounds that have neurotrophic activity but which lack inhibitory action at the protein phosphatase calcineurin and therefore which have no immunosuppressive activity.

It has been suggested in WO-A-96/40140 and WO-A-96/40633 that the neurotrophic effect of these compounds is mediated, at least in part, by a high affinity interaction with the FK-506 binding proteins, such as FKBP-12, or FKBP-52. However, the mechanism by which this interaction with FKBP-type immunophilins results in a neurotrophic effect is at present unknown. The range of neurotrophic activity that can be realised through this neurotrophic/non-immunosuppressant class of compounds has been explored and it has been found that axon regeneration can be promoted after facial nerve crush and sciatic nerve crush in the rat. It has also been observed that the functional regeneration of dopamine neurons damaged with the toxin MPTP was promoted by the compounds disclosed therein in mice. Additionally, it was reported that restoration of striatal innervation in the rat was promoted by the compounds disclosed therein following 6-hydroxydopamine lesioning of dopaminergic neurons (see Hamilton & Steiner, Current Pharmaceutical Design, 1997, 3, 405-428).

It has now been found that the present compounds are neurotrophic agents which have an affinity for FKBP-type immunophilins. In particular, they are potent inhibitors of the enzyme activity and especially of the cis-trans prolyl